Notice of Allowability	Application No.	Applicant(s)	
	10/693,161	JEPPESEN ET AL.	
	Examiner	Art Unit	
	Anthony J. Paviglianiti	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *preliminary amendment filed August 24, 2005*.

2. ☒ The allowed claim(s) is/are *1 - 36, 39 - 40, 42 - 43, 45, 47 - 49, 52 and 53, as amended*.

3. ☐ The drawings filed on _____ are accepted by the Examiner.

4. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☒ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date 1/8/04
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

DETAILED ACTION

Claims 1 – 47 were pending in the original application and were subject to the restriction requirement below. Applicant elected **Claims 1 – 43**, and **Claims 44 – 47** were initially withdrawn pursuant to 37 C.F.R. §1.142(b) as being drawn to a non-elected invention; however, upon searching the art and finding certain product claims to be free of the art and allowable, the examiner expressly withdrew the restriction requirement and the entire application was examined for patentability. Applicant's Preliminary Amendments to the Claims, dated August 24, 2005, have been entered, cancelling **Claims 37, 38, 41** and **44**, and adding new **Claims 48 – 53**. No new matter was found. Accordingly, **Claims 1 – 36, 39 – 40, 42 – 43** and **45 – 53** are pending in the application. An Examiner's Amendment authorized by applicant follows the analysis below.

Priority

This application claims benefit of U.S. Provisional Application No. 60/423,467 (filing date November 4, 2002).

Acknowledgement is made of applicant's claim to foreign priority under 35 U.S.C. §§119(a) – (d), by Denmark Patent Application No. 2002 01631 (filing date October 28, 2002) and Denmark Patent Application No. 2003 00793 (filing date May 26, 2003).

Information Disclosure Statement

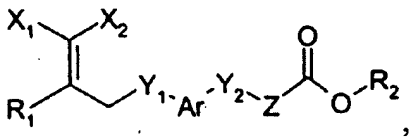
The Information Disclosure Statement filed on January 8, 2004, is in compliance with 37 C.F.R. §1.97, and was considered by the examiner.

Election/Restrictions

The Markush groups set forth in the claims include both independent and distinct inventions, and patentably distinct compounds (or species) within each invention. However, this

application discloses and claims a plurality of patentably distinct inventions far too numerous to list individually. Moreover, each of these inventions contains a plurality of patentably distinct compounds, also far too numerous to list individually. **For these reasons provided below, restriction to one of the following inventions is required under 35 U.S.C. 121,** wherein an Invention is a set of patentably distinct inventions of a broad statutory category (e.g., compounds, methods of use, methods of making, etc.):

I. **Claims 1 – 43**, drawn to compounds and compositions of formula (I),



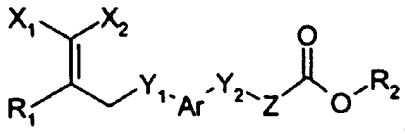
, as depicted in **Claim 1**, classified in Class 560, subclasses 17 and 61; Class 562, subclass 468; and other classes and subclasses.

II. **Claims 44 – 47**, drawn to methods of treatment using the compounds of Formula (I), classified in Class 514, subclasses 543, 571, 461, and other subclasses.

In addition to an election of one of the above Groups, restriction is further required under 35 U.S.C. §121 as follows:

In accordance with the decisions in In re Harnisch, 631 F.2d 716, 206 USPQ 300 (CCPA 1980) and Ex parte Hozumi, 3 USPQ2d 1059 (Bd. Pat. App & Int. 1984), restriction of a Markush group is proper where the compounds with the group either (1) do not share a common utility, or (2) do not share a substantial structural feature disclosed as being essential to that utility. In addition, a Markush group may encompass a plurality of independent and distinct inventions where two or more members are so unrelated and diverse that a prior art reference anticipating the claim with respect to one of the members would not render the claim obvious under 35 U.S.C. §103 with respect to the other member(s).

Therefore, when either of **Groups I or II** is elected, **an election of a single compound of general formula (I) is further required**, including an exact definition of each substitution on the base molecule [i.e., general formula (I)], wherein a single member at each substituent group is selected. For example, if the base molecule of general formula (I),



, has substituent groups $\mathbf{X_1}$ and $\mathbf{X_2}$ which are recited to be "aryl or heteroaryl, each of which is optionally substituted… ," then applicant must select a single substituent representing $\mathbf{X_1}$ and $\mathbf{X_2}$, such as: "$\mathbf{X_1}$ and $\mathbf{X_2}$ are each a phenyl group," as well as specific values at every other variable position, so that a single identifiable compound is selected.

Further, if **Group II** is elected, then **election of a specific method of use, *along with an elected compound of general formula (I)*, is required**; for example, a method of treating:

A. Type I diabetes;

B. Type II diabetes;

C. obesity; etc., using an "elected" compound of general formula (I).

In the instant case, upon election of a single compound, the Office will review the claims and disclosure to determine the scope of the independent invention encompassing the elected compound (compounds which are so similar as to be within the same inventive concept and reduction to practice). The scope of an independent invention will encompass all compounds within the scope of the claim which fall into the same class and subclass as the elected compound, but may also include additional compounds which fall in related subclasses.

Examination will then proceed on the elected compound and the entire scope of the invention encompassing the elected compound as defined by common classification. A clear

statement of the examined invention, defined by those class(es) and subclass(es) will be set forth in the first action on the merits.

Note that the restriction requirement will not be made final until such time as Applicant is informed of the full scope of compounds along with (if appropriate) the process of using or making the compounds under investigation. This will be set forth by reference to specific class(es) and subclass(es) examined.

Should Applicant traverse on the ground that the compounds are not patentably distinct, Applicant should submit evidence or identify such evidence now of record showing the compounds to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. §103(a) of the other invention.

All compounds falling outside of the class(es) and subclass(es) of the selected compound and any other subclass encompassed by the election above will be directed to non-elected subject matter and will be withdrawn from consideration under 35 U.S.C. §121 and 37 C.F.R. §1.142(b). Applicant may reserve the right to file divisional applications on the remaining subject matter. The provisions of 35 U.S.C. §121 apply with regard to double patenting covering divisional applications.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. §1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 C.F.R. §1.48(b) and by the fee required under 37 C.F.R. §1.17(i).

If desired upon election of a single compound, applicants can review the claims and disclosure to determine the scope of the invention and can set forth a group of compounds which are so similar within the same inventive concept and reduction to practice. Markush claims must be provided with support in the disclosure for each member of the Markush group. See MPEP §608.01(p). Applicant should exercise caution in making a selection of a single member for each substituent group on the base molecule to be consistent with the written description.

Rationale Establishing Patentable Distinctiveness Within Each Group

Each Group listed above is directed to or involves the use of compounds which are recognized in the art as being distinct from one another because of their diverse chemical structure, their different chemical properties, modes of action, different effects and reactive conditions (MPEP §806.04, MPEP §808.01). Additionally, the level of skill in the art is not such that one invention would be obvious over the other invention (Group); i.e., they are patentable over each other. Chemical structures which are similar are presumed to function similarly, whereas chemical structures that are not similar are not presumed to function similarly. The presumption even for similar chemical structures though is not irrebuttable, but may be overcome by scientific reasoning or evidence showing that the structure of the prior art would not have been expected to function as the structure of the claimed invention. Note that in accordance with the holding of Application of Papesch, 50 CCPA 1084, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and In re Lalu, 223 USPQ 1257 (Fed. Cir. 1984), chemical structures are patentably distinct where the structures are either not structurally similar, or the prior art fails to suggest a function of a claimed compound would have been expected from a similar structure.

The above Groups represent general areas wherein the inventions are independent and distinct, each from the other, because of the following reasons:

Group I and **Group II** are related as products and methods of using the products. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially-different process of using that product. MPEP §806.05(h). Applying this rule to the instant case, the claimed method of treating type II diabetes, for example, may be practiced with a materially-different product than the compounds of Formula (I), such as the product "metformin." See, e.g., Tiikkainen, M., et al., "Effects of Rosiglitazone and Metformin on Liver Fat Content, Hepatic Insulin Resistance, Insulin Clearance, and Gene Expression in Adipose Tissue in Patients with Type 2 Diabetes," Diabetes, vol. 53, pages 2169-2176 (August 2004), at page 2169, col. 1, lines 2 – 3. **Group I** and **Group II** are therefore separate and distinct inventions for which restriction is appropriate.

In addition, because of the several classes and subclasses with each of the two Groups, and the divergent searches of the prior art that would be required for examination of all the inventions, a serious burden is imposed upon the examiner to perform a complete search of the defined areas. Therefore, for the reasons given above, the restriction set forth is proper, and not to restrict would impose a serious burden in the examination of this application.

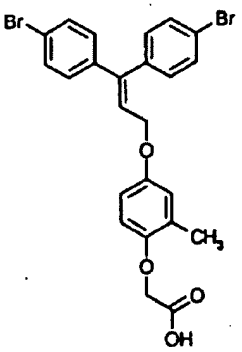
Advisory of Rejoinder

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to

final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

During a telephone conversation with Rosemarie Orescan, Esq., on July 28, 2005, the above restriction requirements were discussed, and applicant provisionally elected the invention of Group I, and the compound {4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-2-methyl-



phenoxy} acetic acid, (Specification at page 57, "Example 10"). [Note: after the elected invention was searched – see below – the restriction requirement was subsequently expressly withdrawn by the examiner].

Applicant is advised that the reply to this requirement to be complete must include an election of the Invention to be examined even though the requirement be traversed. 37 C.F.R. §1.143.

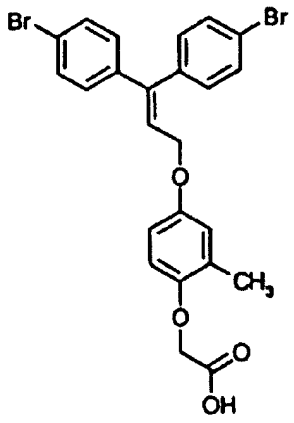
Applicant is further advised that a reply to this requirement must identify the specific compound that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Rejoinder of process claims and withdrawal of restriction requirement

Upon a finding that certain products of genus Formula (I) are free of the prior art and allowable (see "Prior Art Searched" below), the process claims, **Claims 44 – 47**, which had been previously withdrawn by applicant pursuant to 37 C.F.R. §1.142(b) as drawn to a non-elected invention, are hereby **expressly rejoined** for examination for patentability, commensurate in scope with the allowable compounds in **Claim 1**.

Scope of Prior Art Searched

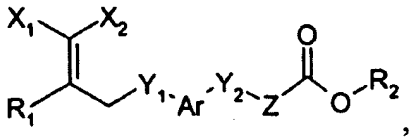
1) The elected compound

The elected compound, {4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-2-methyl-phenoxy} acetic acid, 

, was searched and was found to be free of the prior art. Consequently, the search of the art was expanded beyond the elected compound, as described below.

2) ***Expansion of search of the art to compounds within same or related class/subclass as elected compound***

The search of the art was expanded to include those compounds of Formula (I)



, represented within the same class and subclass or related class as the elected compound, per the original restriction requirement described above. Specifically, the following values for the variables in Formula (I) were initially searched:

$\mathbf{X_1}$ is *phenyl*, optionally substituted by one of more substituents selected from halogen, hydroxy, cyano, amino, carboxy, C_{1-6} alkyl, C_{3-6}-cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aralkyl, heteroaralkyl, C_{1-6} alkoxy, C_{3-6}-cycloalkoxy, aryloxy, aralkoxy, heteroaralkoxy, C_{1-6} alkylthio, arylthio, C_{3-6}-cycloalkylthio, C_{1-6}-alkylcarbonyl, arylcarbonyl, C_{1-6}-alkylsulfonyl, C_{1-6}-alkyl-sulfonyloxy, arylsulfonyl, arylsulfonyloxy, C_{1-6}-alkylamido, arylamido, C_{1-6}-alkylaminocarbonyl, C_{1-6} alkylamino, C_{1-6}-dialkylamino or C_{3-6}-cycloalkylamino each of which is optionally substituted with one or more halogens;

$\mathbf{X_2}$ is *phenyl*, optionally substituted by one of more substituents selected from halogen, hydroxy, cyano, amino, carboxy, C_{1-6} alkyl, C_{3-6}-cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aralkyl, heteroaralkyl, C_{1-6} alkoxy, C_{3-6}-cycloalkoxy, aryloxy, aralkoxy, heteroaralkoxy, C_{1-6} alkylthio, arylthio, C_{3-6}-cycloalkylthio, C_{1-6}-alkylcarbonyl, arylcarbonyl, C_{1-6}-alkylsulfonyl, C_{1-6}-alkyl-sulfonyloxy, arylsulfonyl, arylsulfonyloxy, C_{1-6}-alkylamido, arylamido, C_{1-6}-alkylaminocarbonyl, C_{1-6} alkylamino, C_{1-6}-dialkylamino or C_{3-6}-cycloalkylamino each of which is optionally substituted with one or more halogens;

Ar is *arylene*, optionally substituted with one or more substituents selected from halogen, hydroxy, cyano, C_{1-6} alkyl, C_{3-6}-cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, C_{1-6} alkoxy, C_{3-6}-cycloalkoxy, aryloxy, aralkoxy, heteroaralkoxy, C_{1-6} alkylthio, arylthio, or C_{3-6}-cycloalkylthio, each of which is optionally substituted with one or more halogens [note: The arylene group was searched where the linking groups $\mathbf{Y_1}$ and $\mathbf{Y_2}$ were attached *ortho*, *meta*, or *para* to the single-ring arylene group, where applicable].

$\mathbf{Y_1}$ is O or S;

$\mathbf{Y_2}$ is O or S;

Z is $-(CH_2)_n-$, wherein **n** is 1, 2 or 3;

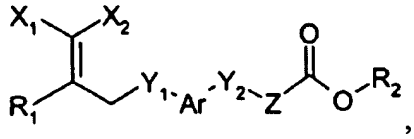
$\mathbf{R_1}$ is hydrogen, halogen, or a substituent selected from C_{1-6} alkyl, C_{3-6}-cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aralkyl, heteroaralkyl, C_{1-6} alkoxy, C_{3-6}-cycloalkoxy, aryloxy, aralkoxy, heteroaralkoxy, C_{1-6} alkylthio, arylthio, or C_{3-6}-cycloalkylthio, each of which is optionally substituted with one or more halogens;

$\mathbf{R_2}$ is hydrogen, C_{1-6} alkyl, C_{3-6}-cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{4-6} alkenynyl or aryl.

Using the above limitations for variables $\mathbf{X_1}$, $\mathbf{X_2}$, **Ar**, $\mathbf{Y_1}$, $\mathbf{Y_2}$, **Z**, $\mathbf{R_1}$ **and** $\mathbf{R_2}$, the compounds of Formula (I) were searched and found free of the prior art of record, so the search of the art was then expanded beyond the compounds within the same or related classes and subclasses as the elected compound, as described below.

3) ***Further expansion of search of art beyond related class/subclass of elected compound***

The search of the art was expanded beyond the scope of the elected compound and the classes and subclasses of the elected compound to encompass several other classes and

subclasses for which examples had been provided in the Claims; specifically, to those compounds encompassed within Formula (I)  , wherein:

X_1 is *phenyl, thienyl, benzothienyl, furyl,* or *benzofuranyl*, optionally substituted by one of more substituents selected from halogen, hydroxy, cyano, amino, carboxy, C_{1-6} alkyl, C_{3-6}-cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aralkyl, heteroaralkyl, C_{1-6} alkoxy, C_{3-6}-cycloalkoxy, aryloxy, aralkoxy, heteroaralkoxy, C_{1-6} alkylthio, arylthio, C_{3-6}-cycloalkylthio, C_{1-6}-alkylcarbonyl, arylcarbonyl, C_{1-6}-alkylsulfonyl, C_{1-6}-alkyl-sulfonyloxy, arylsulfonyl, arylsulfonyloxy, C_{1-6}-alkylamido, arylamido, C_{1-6}-alkylaminocarbonyl, C_{1-6} alkylamino, C_{1-6}-dialkylamino or C_{3-6}-cycloalkylamino each of which is optionally substituted with one or more halogens;

X_2 is *phenyl, thienyl, benzothienyl, furyl,* or *benzofuranyl*, optionally substituted by one of more substituents selected from halogen, hydroxy, cyano, amino, carboxy, C_{1-6} alkyl, C_{3-6}-cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aralkyl, heteroaralkyl, C_{1-6} alkoxy, C_{3-6}-cycloalkoxy, aryloxy, aralkoxy, heteroaralkoxy, C_{1-6} alkylthio, arylthio, C_{3-6}-cycloalkylthio, C_{1-6}-alkylcarbonyl, arylcarbonyl, C_{1-6}-alkylsulfonyl, C_{1-6}-alkyl-sulfonyloxy, arylsulfonyl, arylsulfonyloxy, C_{1-6}-alkylamido, arylamido, C_{1-6}-alkylaminocarbonyl, C_{1-6} alkylamino, C_{1-6}-dialkylamino or C_{3-6}-cycloalkylamino each of which is optionally substituted with one or more halogens;

Ar is *arylene*, optionally substituted with one or more substituents selected from halogen, hydroxy, cyano, C_{1-6} alkyl, C_{3-6}-cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, C_{1-6} alkoxy, C_{3-6}-cycloalkoxy, aryloxy, aralkoxy, heteroaralkoxy,

C_{1-6} alkylthio, arylthio, or C_{3-6}-cycloalkylthio, each of which is optionally substituted with one or more halogens [note: The arylene group was searched where the linking groups $\mathbf{Y_1}$ and $\mathbf{Y_2}$ were attached *ortho*, *meta*, or *para* to the single-ring arylene group, where applicable].

$\mathbf{Y_1}$ is O or S;

$\mathbf{Y_2}$ is O or S;

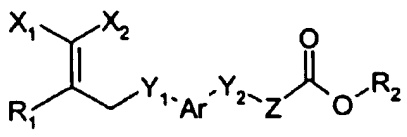
Z is $-(CH_2)_n-$, wherein **n** is 1, 2 or 3;

$\mathbf{R_1}$ is hydrogen, halogen, or a substituent selected from C_{1-6} alkyl, C_{3-6}-cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aralkyl, heteroaralkyl, C_{1-6} alkoxy, C_{3-6}-cycloalkoxy, aryloxy, aralkoxy, heteroaralkoxy, C_{1-6} alkylthio, arylthio, or C_{3-6}-cycloalkylthio, each of which is optionally substituted with one or more halogens;

$\mathbf{R_2}$ is hydrogen, C_{1-6} alkyl, C_{3-6}-cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{4-6} alkenynyl or aryl.

The compounds of Formula (I) encompassed by the limitations of variables $\mathbf{X_1}$, $\mathbf{X_2}$, **Ar**, $\mathbf{Y_1}$, $\mathbf{Y_2}$, **Z**, $\mathbf{R_1}$ and $\mathbf{R_2}$ (as defined above) were found to be free of the prior art of record, so the search of the art was expanded still further.

*4) **Expansion of search where X_1 and X_2 are any 5-, 6-, or 10-membered heteroaryl groups containing a single oxygen or sulfur heteroatom***

The search of the art was then expanded still further to encompass other classes and subclasses for which support had been disclosed in the Claims: all compounds encompassed within Formula (I)  wherein:

X_1 is *phenyl, thienyl, benzothienyl, furyl, benzofuranyl*, or a *5-, 6- or 10-membered heteroaryl having one heteroatom selected from O or S*, optionally substituted by one of more substituents selected from halogen, hydroxy, cyano, amino, carboxy, C_{1-6} alkyl, C_{3-6}-cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aralkyl, heteroaralkyl, C_{1-6} alkoxy, C_{3-6}-cycloalkoxy, aryloxy, aralkoxy, heteroaralkoxy, C_{1-6} alkylthio, arylthio, C_{3-6}-cycloalkylthio, C_{1-6}-alkylcarbonyl, arylcarbonyl, C_{1-6}-alkylsulfonyl, C_{1-6}-alkyl-sulfonyloxy, arylsulfonyl, arylsulfonyloxy, C_{1-6}-alkylamido, arylamido, C_{1-6}-alkylaminocarbonyl, C_{1-6} alkylamino, C_{1-6}-dialkylamino or C_{3-6}-cycloalkylamino each of which is optionally substituted with one or more halogens;

X_2 is *phenyl, thienyl, benzothienyl, furyl, benzofuranyl*, or a *5-, 6- or 10-membered heteroaryl having one heteroatom selected from O or S*, optionally substituted by one of more substituents selected from halogen, hydroxy, cyano, amino, carboxy, C_{1-6} alkyl, C_{3-6}-cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aralkyl, heteroaralkyl, C_{1-6} alkoxy, C_{3-6}-cycloalkoxy, aryloxy, aralkoxy, heteroaralkoxy, C_{1-6} alkylthio, arylthio, C_{3-6}-cycloalkylthio, C_{1-6}-alkylcarbonyl, arylcarbonyl, C_{1-6}-alkylsulfonyl, C_{1-6}-alkyl-sulfonyloxy, arylsulfonyl, arylsulfonyloxy, C_{1-6}-alkylamido, arylamido, C_{1-6}-alkylaminocarbonyl, C_{1-6} alkylamino, C_{1-6}-dialkylamino or C_{3-6}-cycloalkylamino each of which is optionally substituted with one or more halogens;

Ar is *arylene*, optionally substituted with one or more substituents selected from halogen, hydroxy, cyano, C_{1-6} alkyl, C_{3-6}-cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, C_{1-6} alkoxy, C_{3-6}-cycloalkoxy, aryloxy, aralkoxy, heteroaralkoxy, C_{1-6} alkylthio, arylthio, or C_{3-6}-cycloalkylthio, each of which is optionally substituted

with one or more halogens [note: The arylene group was searched where the linking groups $\mathbf{Y_1}$ and $\mathbf{Y_2}$ were attached *ortho*, *meta*, or *para* to the single-ring arylene group, where applicable].

$\mathbf{Y_1}$ is O or S;

$\mathbf{Y_2}$ is O or S;

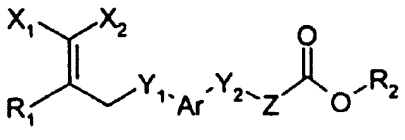
Z is $-(CH_2)_n-$, wherein **n** is 1, 2 or 3;

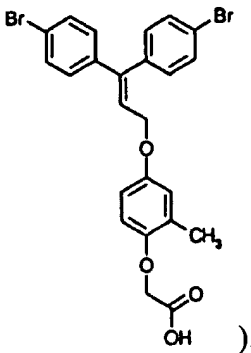
$\mathbf{R_1}$ is hydrogen, halogen, or a substituent selected from C_{1-6} alkyl, C_{3-6}-cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aralkyl, heteroaralkyl, C_{1-6} alkoxy, C_{3-6}-cycloalkoxy, aryloxy, aralkoxy, heteroaralkoxy, C_{1-6} alkylthio, arylthio, or C_{3-6}-cycloalkylthio, each of which is optionally substituted with one or more halogens;

$\mathbf{R_2}$ is hydrogen, C_{1-6} alkyl, C_{3-6}-cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{4-6} alkenynyl or aryl.

As a result of this series of searches of the art, all compounds encompassed within Formula (I), where $\mathbf{X_1}$, $\mathbf{X_2}$, **Ar**, $\mathbf{Y_1}$, $\mathbf{Y_2}$, **Z**, $\mathbf{R_1}$ and $\mathbf{R_2}$ were defined as above, were found to be free of the prior art of record and thus allowable.

Analysis of Claimed Methods of Use

Claim 45 (as amended) of the present invention claims a method for treating type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance or obesity by using compounds having the general chemical structure  as defined in



Claim 1 (for example, the compound). Likewise, **Claim 42** (as amended) claims a "pharmaceutical composition for the treatment of type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance or obesity" by using a compound of **Claim 1** and a carrier or excipient. In this instance, the intended uses impart an additional limitation to **Claim 42**, which were also examined for enablement. See MPEP §2164.01(c) ("when a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation").

The compounds of the present invention are disclosed in the Specification as having activity as agonists of Peroxisome Proliferator-Activated Receptors (PPARs). See, e.g., Specification at p. 1, lines 11 – 14; p. 15, lines 27 – 30; p. 37, line 15 to page 38, line 24; and page 95, line 1 to page 96, line 24 (description of methodology). **Peroxisome Proliferator-Activated Receptors (PPARs)** are a subfamily of nuclear receptors which, among other things, are involved in the storage and catabolism of dietary fats. See, e.g., Willson, T., et al., "The PPARs: From Orphan Receptors to Drug Discovery," J. Med. Chem., vol. 43(4), pages 527 – 550 (Feb. 2000), at p. 527, col. 1, lines 25 – 28. At the time of this application, three PPAR isotypes had been identified: PPARα, PPARδ (also known as PPARβ in some references), and PPARγ. See Kersten, S., et al., "Roles of PPARs in health and disease," Nature, vol. 405, pages 421 – 424 (May 2000), at p. 421, col. 1, lines 14 – 19, et seq.

At the time of this application, PPAR agonists were known in the art for the treatment of diabetes, insulin resistance, impaired glucose tolerance and obesity, and therapeutic agents of this kind were already in clinical use or clinical trials as antidiabetic agents. See, e.g., Kaplan, F., et al., "PPARs, Insulin Resistance and Type 2 Diabetes," J. Cardiovasc. Risk, vol. 8(4), pages 211-217 (Aug. 2001), at p. 213, col. 1, lines 23 – 34 and 37 – 52; Berger, J., and Wagner, J., "Physiological and Therapeutic Roles of Peroxisome Proliferator-Activated Receptors," Diabetes Technology & Therapeutics, vol. 4(2), pages 163 – 174 (2002), at p. 166 (Table 1), and p. 167, col. 1, line 24, et seq.; Fruchart, J., "PPAR and Cardiovascular Risk: Overview," J. Cardiovasc. Risk, vol. 8(4), pages 185 - 186 (Aug. 2001), at p. 185, lines 13 – 20; Jones, B., "Peroxisome Proliferative-Activated Receptor (PPAR) Modulators: Diabetes and Beyond," Medicinal Research Reviews, vol. 21(6), pages 540 – 552 (Nov. 2001), at p. 541, lines 7 – 30, and p. 547 (Table II); Vamecq, J. and Latruffe, N., "Medical significance of peroxisome proliferator-activated receptors," The Lancet, vol. 354, pages 141 – 148 (July 10, 1999), at p. 146 ("Obesity and diabetes"); Torra, I., et al., "Peroxisome proliferator-activated receptors: from transcriptional control to clinical practice," Curr. Opin. Lipidol., vol. 12, pages 245 – 254 (2001), at p. 250, col. 2, lines 9 – 18 and p. 245, lines 5 – 7 (obesity, diabetes and insulin resistance); Michalik, L., and Wahli, W., "Peroxisome proliferator-activated receptors: three isotypes for a multitude of functions," Curr. Opin. Biotechnology, vol. 10, pages 564 – 570 (1999), at p. 565, lines 17 – 21 and Fig. 1; Miller, A., and Etgen, G., "Novel peroxisome proliferator-activated receptor ligands for type 2 diabetes and the metabolic syndrome," Expert Opin. Investig. Drugs, vol. 12(9), pages 1489 – 1500 (2003), at p. 1490, col. 2, lines 2 – 21 and p. 1492, col. 1, lines 17 – 48; Wahli, W., "Peroxisome Proliferator-Activated Receptors (PPARs): from metabolic control to epidermal

wound healing," Swiss Med. Weekly, vol. 132, pages 83 – 91 (2002), at p. 86, col. 1, lines 4 – 27; Everett, L., et al., "The role of hepatic peroxisome proliferator-activated receptors (PPARs) in health and disease," Liver, vol. 20, pages 191 – 199 (2000), at p. 191, lines 1 – 14; Mital, A., "PPARs: Nuclear Receptors for Antidiabetics," CRIPS, vol. 3(1), pages 5 – 8 (Jan.-Mar. 2002), at p. 8, col. 1, lines 4 – 14; and Liu, K., et al., "Identification of a Series of PPAR γ/δ Dual Agonists via Solid-Phase Parallel Synthesis," Bioorg. Med. Chem. Lett., vol. 11, pages 2959 – 2962 (Nov. 2001), page 2959, col. 2, lines 10 – 12.

For these reasons, the written disclosure in the Specification regarding the use of the compounds and compositions of the present invention for treatment of diabetes, insulin resistance, impaired glucose tolerance and obesity, in addition to what was already known in the art at the time of the application about the role of PPAR agonists in these diseases, was determined to be enabling for the person of skill in the art to make and use the invention as claimed in **Claim 42** and **Claim 45**.

Examiner's Amendment to Claims

An examiner's amendment to the record appears below. Should the changes and additions be unacceptable to applicant, an amendment may be filed as provided by 37 C.F.R. §1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Agreement for the following examiner's amendment was reached in a telephone interview with Rosemarie R. Wilk-Orescan, Esq., on August 25, 2005, who authorized the following amendments:

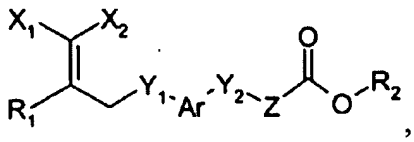
Delete **Claim 46**.

Delete **Claim 50**.

Delete **Claim 51**.

A summary of this telephone interview may also be found on USPTO Form PTOL-413, dated August 25, 2005. It is not necessary for applicant to provide a separate record of the substance of the telephone interview of August 25, 2005.

Reasons for Allowance

The following is an examiner's statement of reasons for allowance: The present invention is directed to certain chemical compounds and compositions having the general formula  , with variables $\mathbf{X_1}$, $\mathbf{X_2}$, $\mathbf{R_1}$, $\mathbf{R_2}$, $\mathbf{Y_1}$, $\mathbf{Y_2}$, **Z**, and **Ar** as defined in **Claim 1** (as amended), which are disclosed as agonists for selected isotypes of Peroxisome Proliferator-Activated Receptors (PPAR), and a method of using these compounds to treat type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance or obesity.

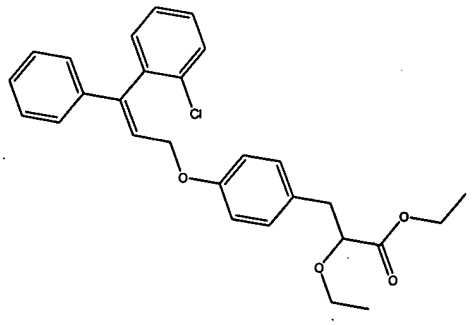
The amended **Title**, submitted by applicant in the Preliminary Amendment dated August 24, 2005, ("Peroxisome Proliferator Activated Receptor-Active Arylene Acetic Acid Derivatives"), is adequately descriptive of the invention, and is accepted.

The amended **Abstract**, as submitted by applicant in the Preliminary Amendment dated August 24, 2005, provides a structure of compounds of general formula (I) which is adequately descriptive of the invention, and is accepted.

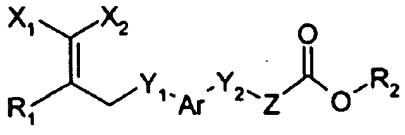
As described in detail in the section "Scope of Prior Art Searched," the search of the art encompassed the entire scope of compounds and compositions, as well as selected methods of use, as defined in **Claims 1 – 36, 39 – 40, 42 – 43, 45, 47 – 49, 52** and **53**, as amended). The

compounds and compositions thus defined were found to be free of the prior art. The structural features which appeared to provide novelty were the limitations in **Claim 1** upon $\mathbf{X_1}$ and $\mathbf{X_2}$, requiring each to be a phenyl group or a 5-, 6- or 10-membered heteroaryl ring having only one heteroatom selected from O or S, not substituted *directly* by another aromatic ring (as in co-pending applications by these inventors), and directly attached to the molecule via an "allyl" group, combined with the limitation that the arylene group ("**Ar**") be linked to the molecule on *both* sides via an oxygen or sulfur atom (i.e., $\mathbf{Y_1}$–**Ar**–$\mathbf{Y_2}$, where $\mathbf{Y_1}$ and $\mathbf{Y_2}$ are limited to O or S). The prior art did not disclose, or render obvious, compounds meeting all of these limitations.

The closest prior art was the compound described in **WO 00/63153** (Murray, et al.), 3-{4-[3-(2-chloro-phenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,



(**WO 00/63153** at page 35, line 35, "Example 3"), which is nearly identical to the compounds and compositions of the present invention, except that the group corresponding to "**Ar**" in the present invention (and in **WO 00/63153**, represented by a phenylene group), is bonded to the molecule via a oxygen atom at the 1-position of the phenyl ring but *via a CH_2 group* at the 4-position; in addition, the "2-ethoxy" substituent in the prior art (attached to the chain containing the ester group) is not within the scope of the limitations of compounds and compositions of the present invention. Thus the above-referenced compound disclosed in **WO 00/63153**, which was determined to be the closest prior art, does not meet or render obvious all of the limitations of the compounds and compositions of the present invention.

The methods of using the claimed compounds and compositions having the general formula  for treatment of diabetes, impaired glucose tolerance, insulin resistance or obesity was determined by the examiner to be supported by the written disclosure in the Specification so as to enable a person of skill in the art to make and use the invention, in view of what was already known in the art at the time about Peroxisome Proliferator-Activated Receptors agonists (see analysis above); and thus are allowable.

Therefore, for the reasons provided in the analyses above, **Claims 1 – 36, 39 – 40, 42 – 43, 45, 47 – 49, 52** and **53**, as amended by applicant on August 24, 2005, and by examiner's amendment, above, are allowable.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should accompany the issue fee. Such submissions should be clearly labeled as "Comments on Statement of Reasons for Allowance."

Conclusion

Claims 1 – 36, 39 – 40, 42 – 43, 45, 47 – 49, 52 and **53** (as amended) are allowable.

Claims 37, 38, 41 and **44** were cancelled by applicant's amendments to the claims filed August 24, 2005.

Claims 46, 50 and **51** were cancelled by Examiner's Amendment (above) as authorized by applicant.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Anthony J. Paviglianiti** whose telephone number is **(571) 272-3107**. The examiner can normally be reached on Monday-Friday, 8:30 a.m. - 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane, can be reached at (571) 272-0699. **The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300. Please note that this is a new central FAX number for all official correspondence.**

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